the stated maximum D_{90} particle size. Support for this insertion can be found in the specification at least at page 7, lines 15-20.

No new matter is introduced and no change in inventorship results from the amendments made herein.

RESPONSE TO OFFICE ACTION DATED JANUARY 10, 2001

Claims 1-50 and 76-83 are pending in the present Application.

Applicant respectfully notes that the Examiner mischaracterized applicant's election in the response to Office Action submitted on August 21, 2000 (Paper No. 7), which identified Claims 11-50 and 76-83 as the elected claims. However, in the interest of facilitating expeditious prosecution, Applicant agrees to continue prosecution of Claims 1-10 as well as the elected claims in the present Application.

1. Rejection under 35 U.S.C. § 112

Claims 77-80 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the use of "such that", for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully points out that MPEP § 2173.05(d), cited by the Examiner, does not relate to a "such that" phrase and believes no indefiniteness results from its use. However, Claims 77-80 have been amended to define particle size by alternative wording having identical meaning. Applicant believes that Claims 77-80 as amended are fully in compliance with 35 U.S.C. § 112 and withdrawal of this rejection is respectfully requested.

2. Rejection under 35 U.S.C § 102

Claims 1-50 stand rejected under 35 U.S.C § 102(a and b) as being anticipated by U.S. Prescribing Information for CELEBREX® (Searle-Pfizer-Pharmacia). The Examiner has offered to reconsider this 35 U.S.C § 102 rejection provided that the applicant submits the date of the reference. Applicant submits herewith a declaration signed by Andrew M. Heard of Pfizer Inc., showing that the date on which the cited reference first became available to the public was later than the priority date of the present application. The cited reference therefore is not prior art. Withdrawal of this 35 U.S.C. § 102 rejection is respectfully requested.

3. Rejection under 35 U.S.C. § 103(a) as unpatentable over Black

Claims 1-50 stand rejected under 35 U.S.C. § 103(a) as unpatentable over EP 0 863 134 (Black). This rejection is respectfully traversed.

The Examiner correctly characterizes Black as teaching that a specific compound which is therapeutically useful as a selective COX-2 inhibitor can be administered orally in the form of tablets, troches, lozenges or capsules. The Examiner also correctly notes that Black teaches (a) that tablets can comprise this specific COX-2 inhibitor as active agent in admixture with conventional excipients, (b) that the active agent can be present in an amount of 10 to 250 mg, (c) that carrier material may vary from about 5% to about 95%, and (d) that the dosage can be administered once or twice a day and will provide an effective $T_{1/2}$ over a 24 hour period.

The Examiner asserts that it would have been "prima facie obvious for one of ordinary skill in this art" to replace Black's COX-2 inhibitor with celecoxib. Applicant respectfully submits that even if it had been, at the time of the present invention, obvious to try this (which is not admitted herein), there is no teaching in Black that would have led a skilled artisan to believe that s/he could formulate, in a particulate form, a selective COX-2 inhibitor, particularly one with such low water solubility as celecoxib, as an orally deliverable composition having a relative bioavailability not less than about 50% by comparison with an oral celecoxib solution at the same dosage rate, as required by Claim 1 as amended herein.

Black teaches that his specific COX-2 inhibitor provides an effective $T_{1/2}$ (half life) over a 24 hour period. Importantly, however, half life, or the measure of time required for concentration of a particular drug in blood or plasma to decrease by one half, is a characteristic that depends to a great extent on the particular drug in that it reflects metabolic processes and/or excretion of the drug, but is not strongly affected by the way the drug is formulated. The formulation can greatly affect the rate and extent of absorption of the drug into the bloodstream, but once in the bloodstream the half life of the drug is largely independent of the formulation. Black is silent on the question of bioavailability, which is a measure of drug absorption into the bloodstream and which, as pointed out immediately above, is formulation-dependent. See, for example, Ansel *et al.* (1995): Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Edition, pages

71-72 (copy attached), which states:

"If equivalent doses of drug in different formulation produce different AUC values, differences exist in the extent of absorption between the formulations."

Id., at page 73 (copy attached):

"It has become well established that the rate and extent to which a drug in a dosage form becomes available for biologic absorption or utilization depends in great measure upon the materials used in the formulation.... Thus, the same drug when formulated in different dosage forms may be found to possess different bioavailability characteristics and hence exhibit different clinical effectiveness."

The present Application discloses that celecoxib, a drug of very low water solubility, can unexpectedly be formulated in particulate form, for example in a tablet or capsule, and yet provide a bioavailability upon oral administration not less than about 50% of that provided by a solution of celecoxib in a suitable solvent, orally administered at the same dose.

In this regard, the Examiner's attention is drawn to Tables 11-2C and 11-2D on page 50 of the specification, in particular to the pharmacokinetic parameter indicated as "Bioavailability (%)". It will be seen that an orally administered unformulated celecoxib capsule (F) exhibited a bioavailability of only 16.9% and that an orally administered celecoxib solution formulation (E) exhibited a bioavailability of 62.4% and 89.4% in female and male dogs respectively. These bioavailabilities are by comparison with intravenous infusion. It will further be seen that, of formulations A-D, all having celecoxib in particulate form, at least formulations A, C and D exhibited in both female and male dogs a relative bioavailability not less than about 50% of that exhibited by solution formulation E at the same dose. Formulation B met that standard in male dogs but fell short in female dogs. Formulation D (a fine suspension) surprisingly exhibited substantially similar bioavailability to solution formulation E, which represents a probable maximum level of bioavailability achievable by oral administration.

The Examiner's attention is also drawn to Table 14 on page 55 of the specification, showing formulated capsule compositions of the invention comprising 100 mg or 200 mg celecoxib. Pharmacokinetic parameters (following oral administration in human subjects) of these capsule formulations were compared with celecoxib suspension

formulation D which, as described above, exhibited substantially similar bioavailability to orally delivered celecoxib solution formulation E. Surprisingly, as shown in Table 18B on page 63 of the specification, these capsule formulations exhibited relative bioavailability (as measured by $AUC_{0-\infty}$ or AUC_{0-t}) that was not less than about 50% by comparison with formulation D. Indeed, both capsule formulations exhibited relative bioavailability that was substantially similar to that of formulation D, *i.e.*, close to what is believed to be the maximum achievable by oral administration.

The surprising findings illustrated in the present specification are of great and far-reaching advantage in the art. Discrete solid dosage forms comprising formulated particulate celecoxib can now be provided which exhibit a relative bioavailability not less than about 50%, and more preferably not less than about 70%, by comparison with an orally delivered solution of celecoxib.

Black provides no teaching that would have suggested to one of skill in the art to try making formulations of particulate celecoxib with an expectation of obtaining a relative bioavailability not less than about 50%, by comparison with an orally delivered solution containing the same amount of celecoxib. Even if, for the sake of argument, motivation had existed based on Black for one of skill in the art to try making such formulations, it would not have been with the expectation of obtaining the remarkably favorable results set out in the present specification. Withdrawal of the rejection of Claim 1, as herein amended, under 35 U.S.C. § 103(a) as unpatentable over Black is therefore respectfully requested.

Claims 2-50 incorporate by their dependency on Claim 1 the defined bioavailability property added by amendment to Claim 1. Withdrawal of the rejection of Claims 2-50 under 35 U.S.C. § 103(a) as unpatentable over Black is therefore respectfully requested.

4. Rejection under 35 U.S.C. § 103(a) as unpatentable over Searle-Pfizer-Pharmacia in view of Black

Claims 1-50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Prescribing Information for CELEBREX® (Searle-Pfizer-Pharmacia), in view of Black. This rejection is respectfully traversed.

As pointed out above, the Searle-Pfizer-Pharmacia reference was not publicly

available before the priority date of the present Application and, therefore, is not prior art. Withdrawal of the rejection under 35 U.S.C. § 103(a) as unpatentable over Searle-Pfizer-Pharmacia in view of Black is therefore respectfully requested.

5. Objection to Claims 76 and 81-83

Claims 76 and 81-83 have been found allowable but for their dependency on a rejected base claim. The Examiner has suggested rewriting these in independent form. Applicant may follow this suggestion at a later stage in prosecution; however, as the base claim for each of these objected-to claims has been amended herein to a form which Applicant believes is allowable, no amendment of Claims 76 and 81-83 is presented at this time.

All claims presently in consideration are believed now to be in condition for allowance. No fee is believed payable in connection with the present Amendment and Response to Office Action; however, if it is determined that a fee is payable, please charge Deposit Account No. 19-1025, in the name of G.D. Searle & Co.

Respectfully submitted,

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Attachments
Ansel *et al.* (1995): Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Edition, pages 71-73.
Declaration of Andrew M. Heard.

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Pharmaceutical Dosage Forms and Drug Delivery Systems

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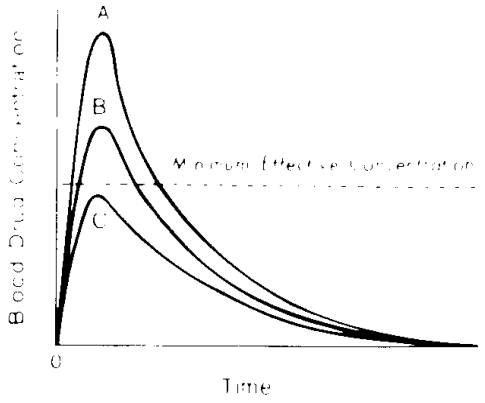

Fig. 3–8. *The influence of dose size on the resultant blood drug concentration time curves when three different doses of the same drug are administered and the rates of drug absorption and elimination are equal after the three doses. A = 100 mg, B = 50 mg, C = 25 mg. (From C.H. Hollenbeck: Concepts in Clinical Pharmacology. Essentials of Bioavailability and Bioequivalence. 1979. The Upjohn Company. Reproduced with permission.)*

formulation "A" permits the greater rate of drug absorption; it allows drug to reach both the MEC and its peak height sooner than drug formulation "B." On the other hand, formulation "B" provides the greater duration of time for drug concentrations maintained above the MEC, 8 hours (from 2 to 10 hours following administration) to 5½ hours (from 30 minutes to 6 hours following administration) for formulation "A." Thus, if a rapid onset of action is desired, a formulation similar to "A" would be preferred. But if a longer duration of action is desired rather than a rapid onset of action, a formulation similar to "B" would be preferred.

In sum, changes in the *rate* of drug absorption will result in changes in the values of both C_{max} and T_{max}. Each product has its own characteristic rate of absorption. When the *rate* of absorption is decreased, the C_{max} is lowered and T_{max} occurs at a later time. If the doses of the drugs are the same and presumed completely absorbed, as in Figure 3–7, the AUC for each is essentially the same.

AREA UNDER THE SERUM CONCENTRATION-TIME CURVE. The area under the curve (AUC) of a concentration-time plot (Fig. 3–4) is considered representative of the total amount of drug absorbed into the circulation following the administration of a single dose of that drug. Equivalent doses of a drug, when fully absorbed, would produce the same AUC. Thus, two curves much unalike in terms of peak height and time of peak, as those in Figure 3–7, may be much alike in terms of area under the curve, and thus in the amount of drug absorbed. As indicated in Figure 3–7, the area under the curve for formulation "A" is 34.4 mcg/mL × hours and for formulation "B" is 34.2 mcg/mL × hours, essentially the same. If equivalent doses of drug in different formulation produce *different* AUC values, differences exist

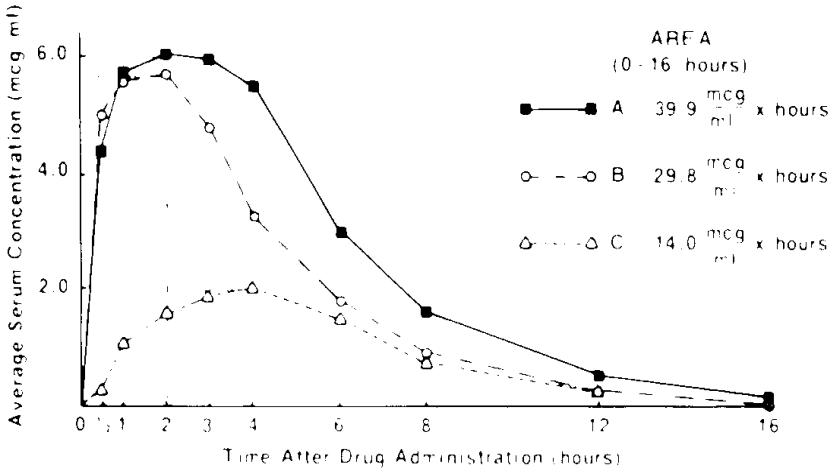

Fig. 3–9. *Serum concentration time curves showing peak height concentrations, peak height times, and areas under the curves for equal amounts of drugs from three different formulations following oral administration. (Courtesy of D.P. Christo and A.R. DiSante. The Upjohn Company.)*

in the extent of absorption between the formulations. Figure 3–9 depicts concentration time curves for three different formulations of equal amounts of drug with greatly different areas under the curve. In this example, formulation "A" delivers a much greater amount of drug to the circulatory system than do the other two formulations. In general, the smaller the AUC, the less drug absorbed.

The area under the curve may be measured mathematically, using a technique known as the trapezoidal rule, and is reported in amount of drug/volume of fluid × time (e.g., mcg/ml × hours; g/100 × hours; etc.).

According to the trapezoidal rule, the area beneath a drug concentration-time curve can be estimated through the assumption that the AUC can be represented by a series of trapezoids (quadrilateral planes having two parallel and two nonparallel sides). The total AUC would be the sum of the areas of the individual trapezoids. The area of each trapezoid is calculated taking $\frac{1}{2}(C_{n-1} + C_n)(t_n - t_{n-1})$, where C_n and t_n are drug concentrations in the blood plasma, or serum, and time, respectively. Ueda demonstrates the use of the trapezoid by the data reproduced in Table 3–3 and plotted into a plasma drug concentration-time curve as shown in Figure 3–10.

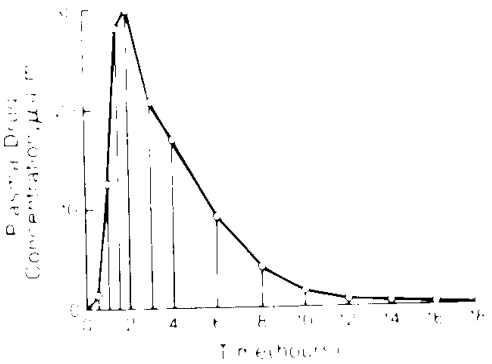

Fig. 3–10. *Estimation of area under the drug concentration time curve using the trapezoidal rule (see Table 3–3 for data). (From C. T. Ueda, "Concepts in Clinical Pharmacology: Essentials of Bioavailability and Bioequivalence" 1979. The Upjohn Company. Reproduced with permission.)*

The fraction (F) (or bioavailability) of an orally administered drug may be calculated by comparison of the AUC after oral administration with that obtained after intravenous administration:

$$F = (AUC)_{oral} / (AUC)_{intravenous}$$

In practice, it would be rare for a drug to be

Table 3–3. Determination of AUC Using the Trapezoidal Rule for the Following Plasma Drug Concentration-Time Data*

Sample (n)	Time (hr)	Plasma Concentration (μg/ml)	AUC (n−1, n) (μg/ml × hr)	
1	0	0		
2	0.5	1	0.5 × 1 × 0.5	0.25
3	1.0	11	0.5 × (1 + 11)	3.00
4	1.5	28	0.5 × (11 + 28) × 1.5	9.75
5	2	30	0.5 × (28 + 30) × 1	14.50
6	3	21	0.5 × (30 + 21) × 2	25.50
7	4	17	0.5 × (21 + 17) × 3	19.00
8	6	6	0.5 × (17 + 6) × 4	23.00
9	8	4	0.5 × (6 + 4) × 6	13.00
10	10	2	0.5 × (4 + 2) × 8	6.00
11	12	1	0.5 × (2 + 1) × 10	3.00
12	18	0	0.5 × (1 + 0) × 12	3.00
			AUC	125.00

* From C. T. Ueda, "Concepts in Clinical Pharmacology: Essentials of Bioavailability and Bioequivalence," 1979. The Upjohn Company. Reproduced with permission.

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completely absorbed into the circulation following oral administration. As noted earlier, many drugs undergo the first pass effect resulting in some degree of metabolic degradation before entering the general circulation. In addition, factors of drug product formulation, drug dissolution, chemical and physical interactions with the gastrointestinal contents, gastric emptying time, intestinal motility, and others contribute to the incomplete absorption of an administered dose of a drug. The oral dosage strengths of many commercial products are based on considerations of the proportion of the dose administered that is expected to be absorbed and available to its site of action in order to produce the desired drug blood level and/or therapeutic response. The **absolute bioavailability** following oral dosing is generally compared to **intravenous dosing**. As examples, the mean oral absorption of a dose of verapamil (Calan) is reported to be 90%; enalapril (Vasotec) 60%; diltiazem (Cardizem) about 40%, and lisinopril (Zestril) about 25%. However, there is large intersubject variability, and the absorbed doses may vary patient-to-patient.

Bioequivalence of Drug Products

A great deal of discussion and scientific investigation has been devoted recently to the problem of determining the equivalence between drug products of competing manufacturers.

It has become well established that the rate and extent to which a drug in a dosage form becomes available for biologic absorption or utilization depends in great measure upon the materials utilized in the formulation and also on the method of manufacture. Thus, the same drug when formulated in *different* dosage forms may be found to possess different bioavailability characteristics and hence exhibit different clinical effectiveness. Further, two seemingly "identical" or "equivalent" products, of the same drug, in the same dosage strength and in the *same* dosage form type, but differing in formulative materials or method of manufacture, may vary widely in bioavailability and thus in clinical effectiveness.

Dissolution requirements for capsules and tablets are included in the USP and are integral to bioavailability. Experience has shown that where bioinequivalence has been found between two supposedly equivalent products, dissolution testing can help to define the product differences. According to the USP, significant bioavailability and bioinequivalence problems may be revealed through dissolution testing and are generally the result of one or more of the following causal factors: the drug's particle size; excessive amounts of the lubricant magnesium stearate in the formulation; coating materials, especially shellac; and inadequate amounts of tablet or capsule disintegrants.

The following terms are used by the Food and Drug Administration to define the type or level of "equivalency" between drug products.[7]

Pharmaceutical equivalents are drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Bioequivalent drug products are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption, and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied.

In addition, the term *therapeutic equivalents* has been used to indicate pharmaceutical equivalents which, when administered to the same individuals in the same dosage regimens, will provide essentially the same therapeutic effect.

DECLARATION

I, Andrew M. Heard, of Chatham, NJ, a citizen of the U.S.A., am an employee of Pfizer Incorporated, a corporation having offices at 235 East 42nd Street, New York, NY. I was intimately involved in launching the web site having as an address www.celebrex.com, and containing information relevant to the pharmaceutical product CELEBREX® which is marketed in the United States by G. D. Searle & Co. (now a unit of Pharmacia Corporation) and Pfizer Incorporated.

I hereby declare that:

(1) the above referenced web site was not live on or before November 30, 1998;

(2) the above referenced web site became live on a launch date that was later than November 30, 1998; and

(3) no information was publicly available via the above referenced web site prior to the launch date of the web site.

I hereby declare that all statements above made of my own knowledge are true; and further that all statements above are made with the knowledge that willful false statements so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code.

.....

Andrew M. Heard

Date March 22, 2001